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APPLICATION NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO.
08/447,118	05/22/95	BURKLY L	BGP-151CP(D)

EXAMINER

18M1/1126

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ART UNIT	PAPER NUMBER
1806	17

DATE MAILED: 11/26/97

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

OFFICE ACTION SUMMARY

☑ Responsive to communication(s) filed on 9/8/97

☑ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 D.C. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), ~~or thirty days~~, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☑ Claim(s) 1-10, 12-18, 21-29 is/are pending in the application.
Of the above, claim(s) 1-9, 21-24 is/are withdrawn from consideration.
☐ Claim(s) _____ is/are allowed.
☑ Claim(s) 10, 12-18 + 25-29 is/are rejected.
☐ Claim(s) _____ is/are objected to.
☐ Claim(s) _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.
☐ The drawing(s) filed on _____ is/are objected to by the Examiner.
☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.
☐ The specification is objected to by the Examiner.
☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.
☐ received in Application No. (Series Code/Serial Number) _____.
☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of Reference Cited, PTO-892
☑ Information Disclosure Statement(s), PTO-1449, Paper No(s). 15
☐ Interview Summary, PTO-413
☐ Notice of Draftperson's Patent Drawing Review, PTO-948
☐ Notice of Informal Patent Application, PTO-152

--SEE OFFICE ACTION ON THE FOLLOWING PAGES--

1. The Amendment filed September 8, 1997 (Paper No. 14) in response to the Office Action of March 4, 1997 (Paper No. 10) is acknowledged and has been entered. Previously pending claims 10, 15, 16, and 18 have been amended, previously pending claims 11 and 19-20 have been cancelled and new claims 25-29 have been added. Claims 10, 12-18 and 25-29 are currently under prosecution.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

3. The response (Paper No. 14) to the restriction requirement of March 4, 1997 (Paper No. 10) has been received. Applicant has elected Group II, claims 10-20 and species 2, claims 12-14, for examination. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP 818.03(a).

4. The following objections are being maintained:

(a) Objection to the Declaration on Page 5, Section 11 of Paper No. 10 is maintained because a new declaration has not been submitted.

(b) Objection to the specification drawn to the drawings on Page 6, Section 13 of Paper No. 10 is maintained because no correction has been made to Figure 5.

5. The following rejections are being maintained:

Claim Rejections - 35 USC § 112

6. Claims 10 and 15-18 remain rejected under 35 USC 112, first paragraph for the reasons previously set forth in Paper No. 10, Section 16, pages 9-11.

Applicant argues that (a) NOD mice are an art recognized animal model for human type I diabetes and presents evidence to that effect, (b) there is no reason to believe that blocking the VLA-4/VCAM-1 interaction in humans would not produce results similar to those in NOD mice, (c) Applicant's assertions that administration of anti-VLA-4 antibodies are useful to treat diabetes-prone mice based on adoptive transfer experiments is validated by the Yang et al reference which discloses experiments in which diabetes-prone mice were administered rat anti-mouse VLA-4 antibodies whereby the onset of diabetes was significantly delayed, and (d) murine monoclonal antibodies have been shown to be therapeutically effective in a number of human settings. The arguments have been noted but have not been found persuasive because, (a) although Applicant presents evidence that the NOD mouse model is an art recognized model of Type I diabetes, it is clear that the cited reference, Bowman et al on page 115, second column, cautions about the use of the NOD mouse model for extrapolation of therapeutic intervention into human disease because of the differences in the mice and humans, that is, the natural history of IDD development in NOD mice is quite predictable, however, this is not true of humans because of the genetic and environmental heterogeneity associated with the natural history of IDD in humans and that it has thus been difficult for clinical investigators to develop diagnostic tools for the early identification of humans destined to develop IDD and further cautions that for these reasons,

studies to prevent (delay or inhibit) onset of IDD in NOD mice (which reads on the enablement of the instant claims) must be carefully analyzed for their applicability to therapeutic intervention in human disease, thus it is clear that the data presented in the instant specification cannot be extrapolated to predict human efficacy *in vivo* because it would be impossible to duplicate the saturation of spleen cells with the desired antibodies prior to onset of the disease, and the results of the instant method could not be predicted from the disclosure, (b) Applicant's stated opinion does not appear to be supported by factual data, either in the disclosure or the literature review (c) differences in administration protocols, including concentrations and timing of injection, makes it difficult to compare the results of the cited study with the instant disclosure and further, although it is clear that chronic administration of anti VLA-4 antibody to neonates prevented the development of diabetes in female NOD mice, it is clear that this treatment cannot be extrapolated to humans since the effects of chronic administration of anti-VLA-4 antibodies, starting at birth, on the homeostasis of VLA-4 associated systems cannot be predicted in humans and (d) the issue raised in the instant rejection is not whether murine monoclonal antibodies have been shown to be therapeutically effective in a number of human settings but rather whether use of the broadly claimed antibody (which reads on the murine) will function in the method as claimed. Further, it was well known in the art at the time the invention was made that there are problems with murine monoclonal antibodies that render their use unpredictable *in vivo* in humans, that is, that the patient's body mounts an

immune response to the murine immunoglobulins which can lead to anaphylaxis or serum sickness and to the neutralization of the administered antibody. Applicant's arguments have not been found persuasive and the rejection is maintained.

7. Claims 10, 12-14 and 16-17 remain rejected under 35 USC 112, first paragraph for the reasons previously set forth in Paper No. 10, Section 17, pages 11-12.

Applicant argues that the rejection is met by deleting "polypeptides and small molecules" from the claims. The argument has been noted but has not been found persuasive because the claims as originally written read on the currently claimed polypeptides and the issues raised in Section 17 are relevant to the specifically recited VCAM and fibronectin polypeptides, that is that, the specification does not address the pharmokinetic properties of VLA4 binding polypeptides nor their cross reactivity nor the differences between *in vivo* human treatment and animal models in terms of the fate and activity of the polypeptides. Applicant's arguments have not been found persuasive and the rejection is maintained.

8. Claims 10 and 12-18 remain rejected under 35 USC 112, first paragraph for the reasons previously set forth in Paper No. 10, Section 19, pages 13-14.

Applicant argues that (a) the claims are directed to delaying the onset of diabetes and (b) it seems highly unlikely that all islet cells would already be dead in such individuals. The argument has been noted but has not been found persuasive because (a) Applicant is arguing limitations not found in the claims

as presently constituted and (b) Applicant's expressed opinion that it seems highly unlikely that all islet cells would already be dead does not address the issue raised in the instant rejection, that is, whether or not the instant method would be predictable in a patient wherein the Islet cells are damaged. Applicant's arguments have not been found persuasive and the rejection is maintained.

9. Claims 10, 12-18 remain rejected under 35 USC 112, first paragraph for the reasons previously set forth in Paper No. 10, Section 20, pages 14-16.

Applicant argues that the method of the invention was shown to treat and not exacerbate the diabetes-like condition in NOD mice. The argument has been noted but has not been found persuasive because animal models do not fully mimic the biology of human patients. Further the issue raised in the instant rejection is not whether the method of the invention treated or exacerbated the diabetes-like condition in NOD mice but rather the unpredictability of the effects of the instant method of treatment on perturbation of the complex regulatory networks involving VLA-4 positive cells in humans. Applicant's arguments have not been found persuasive and the rejection is maintained.

10. Claim 16 remain rejected under 35 USC 112, second paragraph for the reasons previously set forth in Paper No. 10, Section 21, pages 16-20.

As drawn to improper Markush format of claim 16 Applicant argues that the rejection is met by amending claim 16. The argument has been noted but has not been found persuasive because claim 16 has not been amended to recite

"selected from the group consisting or" with the use of the conjunction "and". Applicant's arguments have not been found persuasive and the rejection is maintained.

Double Patenting

11. Claims 10 and 15-18 remain provisionally rejected under 35 U.S.C. § 101 as claiming the same invention as that of claims 10-11, 13, 12-14 and 16 of copending application Serial No. 08/447,098 for the reasons previously disclosed in Paper No. 10, Sections 22-24, pages 20-22.

Applicant argues that the provisional rejection will be met when claims have been allowed in both applications, thus the rejection is maintained since the claims have not been cancelled nor has a terminal disclaimer been filed.

12. All other objections and rejections recited in Paper No. 10 are withdrawn.

New Ground of Rejection

Claim Rejections - 35 USC § 112

13. The specification is further objected to under 35 USC 112, first paragraph, and Claims 10, 12-18 and 25-29 are rejected under 35 USC 112 first paragraph as failing to provide sufficient guidance to enable one skilled in the art to use a method for treatment of diabetes comprising administering an antibody, fragment of such antibody, soluble VCAM-1 polypeptides or fibronectin polypeptides.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with the claims. The claims as broadly written

read on treatment of any and all aspects of diabetes. The specification provides neither guidance on nor exemplification of any aspect of diabetes treatment other than delayed onset of diabetes in a NOD mouse adoptive transfer model. Reasonable correlation must exist between the scope of the claims and scope of enablement set forth, and it cannot be predicted from the disclosure how or whether the instant method will treat any or all aspects of diabetes. Therefore, undue experimentation would be required to enable the claims.

14. Claims 25-29 are rejected under 35 USC 112, first paragraph for the reasons disclosed in Sections 6-11 and in Paper No. 10, Sections 16, 17, 19, 20 and 22-24.

15. Claims 10, 12-18 and 25-29 are rejected under 35 USC 112, second paragraph because claim 10 recites the "a method of treatment.....effective to treat diabetes. The claim is confusing because it is not clear what treatment is being effected, for example, is the output of insulin increased, is the onset of the disease being delayed?

16. No claims allowed.

17. Applicant's amendment necessitated the new grounds of rejection. Accordingly, **THIS ACTION IS MADE FINAL**. See M.P.E.P. § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 C.F.R. § 1.136(a).

A SHORTENED STATUTORY PERIOD FOR RESPONSE TO THIS FINAL ACTION IS SET TO EXPIRE THREE MONTHS FROM THE DATE OF THIS ACTION. IN THE EVENT A FIRST RESPONSE IS FILED

WITHIN TWO MONTHS OF THE MAILING DATE OF THIS FINAL ACTION AND THE ADVISORY ACTION IS NOT MAILED UNTIL AFTER THE END OF THE THREE-MONTH SHORTENED STATUTORY PERIOD, THEN THE SHORTENED STATUTORY PERIOD WILL EXPIRE ON THE DATE THE ADVISORY ACTION IS MAILED, AND ANY EXTENSION FEE PURSUANT TO 37 C.F.R. § 1.136(a) WILL BE CALCULATED FROM THE MAILING DATE OF THE ADVISORY ACTION. IN NO EVENT WILL THE STATUTORY PERIOD FOR RESPONSE EXPIRE LATER THAN SIX MONTHS FROM THE DATE OF THIS FINAL ACTION.

18. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Susan Ungar, PhD whose telephone number is (703) 305-2181. The examiner can normally be reached on Monday through Friday from 7:30am to 4pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lila Feisee, can be reached at (703) 308-2731. The fax phone number for this Art Unit is (703) 308-4242.

Communications via Internet e-mail regarding this application, other than those under 35 USC 132 or which otherwise require a signature may be used by the applicant and should be addressed to lila.feisee@uspto.gov.

All internet e-mail communications will be made of record in the application file. **PTO employees do not engage in Internet communications where there exists a possibility that sensitive information could be identified or exchanged unless the record includes a properly signed express waiver of the confidentiality requirements of USC 122.** This is more clearly set forth in

the Interim Internet Usage Policy published in the Official Gazette of the Patent and Trademark on February 25, 1997 at 1195 OG 89.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Susan Ungar
November 17, 1997

LILA FEISEE
SUPERVISORY PATENT EXAMINER
GROUP 1800